Pediatric Neuroblastoma: Pharmacotherapy Advances for High-Risk and Relapsed/Refractory Disease

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Objectives

• Identify therapeutic options for the treatment of high-risk and relapsed/refractory pediatric neuroblastoma.

• Review clinical data evaluating the use of $^{131}$I-MIBG, ALK inhibitors, and GD2 antibodies in treatment regimens for high-risk and relapsed/refractory pediatric neuroblastoma.

• Outline therapeutic strategies to mitigate adverse events associated with dinutuximab-containing regimens.
Case: KE

- KE is a 7 yo previously healthy female who presents w/ several “knots” on her scalp & orbit, a palpable large mass on RLE, & marked bruising

- Initial Workup:
  - CBC: Hgb 7.2, WBC 4.8, Plt 6, differential unremarkable
  - CT: calcified right adrenal mass
Case, Cont.

• Workup, cont.
  • Urine: VMA = 14.6, HVA = 40
  • BMBx: >90% involvement w/ small blue round cell tumors forming pseudorosettes
    • FISH: MYCN gene amplification

• Diagnosis:
  • Stage 4 neuroblastoma
Outline

- Neuroblastoma 101
- Novel options for upfront management of high-risk disease
  - Dinutuximab
  - ¹³¹I-MIBG
- Novel options for relapsed/refractory disease
  - hu14.18K322A
  - ¹³¹I-MIBG
  - Small molecule inhibitors (crizotinib, alisertib)
Pediatric Neuroblastoma

• Embryonal neoplasm of sympathetic nervous system

• 3rd most common pediatric cancer; most common extracranial solid tumor in children
  • ~700 cases in US annually

• 90% will be diagnosed by 5 years of age
  • Median age of diagnosis: ~18 mo
Clinical Presentation

• Majority present w/ primary abdominal disease
  • Fullness, discomfort, palpable mass

• Signs/symptoms of metastatic disease
  • Periorbital ecchymoses, proptosis
  • Bone pain, cytopenias
  • Bluish, nontender subcutaneous nodules

• Detectable urinary catecholamines (VMA, HVA)
Clinical Presentation

- Majority present w/ primary abdominal disease
  - Fullness, discomfort, palpable mass
- Signs/symptoms of metastatic disease
  - Periorbital ecchymoses, proptosis
  - Bone pain, cytopenias
  - Bluish, nontender subcutaneous nodules
- Detectable urinary catecholamines (VMA, HVA)
- Paraneoplastic syndromes
  - Opsoclonus-myoclonus-ataxia syndrome
  - VIP syndrome

VIP: vasoactive intestinal polypeptide
VMA: Vanillylmandelic acid
HVA: Homovanillic acid

Brodeur et al. Principles and Practice of Pediatric Oncology. 6th edition
## Staging

<table>
<thead>
<tr>
<th>INSS Stage</th>
<th>Proportion of Patients</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>17%</td>
<td>Local tumor w/ complete gross excision</td>
</tr>
<tr>
<td>2</td>
<td>16%</td>
<td>Localized tumor w/ or w/o complete excision but positive ipsilateral node(s)</td>
</tr>
<tr>
<td>3</td>
<td>16%</td>
<td>Unresectable unilateral tumor infiltrating across midline</td>
</tr>
<tr>
<td>4</td>
<td>44%</td>
<td>Dissemination to distant nodes or organs</td>
</tr>
<tr>
<td>4S</td>
<td>7%</td>
<td>Localized tumor w/ dissemination limited to skin, liver, and/or marrow in infants &lt;1yr of age</td>
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</tbody>
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## Prognosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Poor Prognostic Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>INSS Stage</td>
<td>Higher stage disease (except 4S)</td>
</tr>
<tr>
<td>Age</td>
<td>&gt;12-18 mo</td>
</tr>
<tr>
<td>Shimada Histology</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>MYCN Amplification</td>
<td>Amplified</td>
</tr>
<tr>
<td>DNA Ploidy</td>
<td>Diploid</td>
</tr>
</tbody>
</table>

### Risk Classification (COG) | Proportion of Patients | Long-Term Event-Free Survival |
---|---------------------------|--------------------------|
| Low | 40%                       | >95%                     |
| Intermediate | 20%                       | 80-95%                   |
| High | 40%                       | 40-50%                   |

INSS: International Neuroblastoma Staging System
COG: Children’s Oncology Group

Treatment Overview: High-Risk Disease

Induction Chemotherapy → Surgery → Myeloablative Therapy/Autologous HSCT → Radiation → Maintenance Therapy

HSCT: Hematopoietic stem cell transplantation

Brodeur et al. Principles and Practice of Pediatric Oncology. 6th edition
**Historical Standard**

<table>
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<tr>
<th>Design</th>
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<th>Patients</th>
<th>Efficacy</th>
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<tbody>
<tr>
<td>Matthay et al 1999</td>
<td>Multi-center, Phase 3 randomized controlled trial</td>
<td>Randomization #1: Chemo vs auto HSCT Randomization #2: observation vs RA maintenance</td>
<td>Randomization #1: 3yr EFS = 34% vs 22% (p = 0.034), 3yr OS = 43% vs 44% (p = NS) Randomization #2: 3yr EFS = 46% vs 29% (p = 0.027), 3yr OS = 56% vs 50% (p = NS)</td>
</tr>
</tbody>
</table>

*Notes:*
- **HSCT:** Hematopoietic stem cell transplantation
- **RA:** 13-cis retinoic acid (isotretinoin)
- **NS:** non-significant

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Self-Assessment #1

• Which of the following should be a part of KE’s initial treatment course for her high-risk neuroblastoma?

a. Crizotinib
b. $^{131}$I-MIBG
c. Alisertib
d. Dinutuximab
Outline

• Neuroblastoma 101

• Novel options for upfront management of high-risk disease
  • Dinutuximab
  • $^{131}$I-MIBG

• Novel options for relapsed/refractory disease
  • hu14.18K322A
  • $^{131}$I-MIBG
  • Small molecule inhibitors (crizotinib, alisertib)
Dinutuximab

Antibody-Dependent Cellular Cytotoxicity & Complement-Mediated Cytotoxicity
GD2

• Disialoganglioside tumor-associated antigen
  • Tumor expression:
    • Neuroblastomas, melanomas, others
  • Normal tissue expression:
    • Neurons, melanocytes, peripheral sensory nerve fibers

• Dinutuximab binding triggers ADCC and complement-mediated cytotoxicity
Dinutuximab (ch14.18)

- Chimeric monoclonal antibody against GD2

- Approved 3/2015 for high-risk neuroblastoma
  - Combination therapy w/ GM-CSF, IL-2, and 13-cis retinoic acid (isotretinoin)

- Box warnings:
  - Life-threatening infusion reactions
  - Severe neuropathic pain
# Dinutuximab Efficacy

Yu et al. *NEJM* 2010; 363(14):1324-34.

**Induction, auto HSCT, radiation**

**Randomization**

<table>
<thead>
<tr>
<th>RA</th>
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**Design**

Yu et al 2010

Multi-center, Phase 3 randomized controlled trial

**Intervention**

Standard RA maintenance vs dinutuximab immunotherapy

**Patients**

N = 226 pts w/ high-risk neuroblastomas/p auto HSCT w/o progressive disease

**Efficacy**

Stopped early for benefit; 2yr EFS = 66% vs 46% (p = 0.01) 2yr OS = 86% vs 75% (p = 0.02)

ch14.18: dinutuximab  
RA: 13-cis retinoic acid (isotretinoin)  
GM-CSF: granulocyte-macrophage colony stimulating factor  
IL-2: interleukin 2

Yu et al. *NEJM* 2010; 363(14):1324-34.
Dinutuximab Safety

- Grade 3/4 pain = 52%
  - Improved with subsequent cycles
  - Premedicate w/ morphine bolus + infusion

- Capillary leak syndrome = 23%
  - Worse during cycles 2, 4

- Grade 3/4 hypersensitivity = 25%
  - Premedicate w/ APAP, diphenhydramine

APAP: acetaminophen

Yu et al. NEJM 2010; 363(14):1324-34.
Pain Management

- PI guidance:
  - IV morphine 50 mcg/kg, followed by 20-50 mcg/kg/hr during infusion + 2 hours after
    - 25-50 mcg/kg boluses q2h PRN
  - “Consider use of gabapentin or lidocaine”

- Dexmedetomidine?
  - Report of 6 pts receiving adjunctive dexmedetomidine (avg dose 0.17 mcg/kg/hr)
  - Dinutuximab infusion rate interrupted only 1/122 treatment days
  - Hypotension 30%, hypoxemia 8%, bradycardia 4%
$^{131}$I-MIBG

Cytotoxicity;
Radiation-induced bystander effect
$^{131}$I-MIBG

- 90% tumors express norepinephrine transporter (NET)
- MIBG = norepinephrine analogue; actively transported intracellularly via NET
  - TCAs may compete w/ MIBG uptake
- Radiolabeled MIBG $\rightarrow$ cytotoxicity
- Hematologic toxicity; radiation precautions
### $^{131}$I-MIBG Efficacy

#### Upfront Therapy

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<tbody>
<tr>
<td>de Kraker et al 2008</td>
<td>Single center, Phase 1</td>
<td>$^{131}$I-MIBG monotherapy</td>
<td>ORR = 66%; 5yr EFS = 12.2%, 5yr OS = 14.6%</td>
</tr>
<tr>
<td>Kraal et al 2015</td>
<td>Multi-center, single-arm Phase 2</td>
<td>Upfront $^{131}$I-MIBG + topotecan</td>
<td>ORR = 57%; 10yr OS = 6%</td>
</tr>
</tbody>
</table>

ORR: objective response rate

MIBG: metaiodobenzylguanidine

Mayo Clinic Children's Center


$^{131}$I-MIBG Safety

**Upfront Therapy**

- de Kraker et al 2008
  - “Hematological side effects were limited to thrombocytopenia”
  - 1 death attributed to toxic myelosuppression
  - Transient TSH elevations in 45.5% patients

- Kraal et al 2015
  - Grade 3/4 thrombocytopenia = 60%
  - Grade 3/4 neutropenia = 60%

*MIBG: metaiodobenzylguanidine  
ORR: objective response rate*
Case, Revisited

• After induction chemotherapy, surgical removal of her primary, autologous stem cell transplant, and radiation, KE is set to begin immunotherapy with dinutuximab.

• Which of the following pre-medication regimens would be most appropriate for dinutuximab?
Self-Assessment #2

• Which of the following pre-medication regimens would be most appropriate for dinutuximab?

a. Ondansetron, dexamethasone, aprepitant
b. Methylprednisolone, APAP, diphenhydramine
c. Morphine, APAP, diphenhydramine, IV fluids
d. Allopurinol, IV fluids, granisetron
Outline

• Neuroblastoma 101

• Novel options for upfront management of high-risk disease
  • Dinutuximab
  • $^{131}$I-MIBG

• Novel options for relapsed/refractory disease
  • hu14.18K322A
  • $^{131}$I-MIBG
  • Small molecule inhibitors (crizotinib, alisertib)
hu14.18K322A

- Humanized GD2 antibody engineered to reduce pain
  - K322A point mutation $\rightarrow$ decreased complement activation
  - Decreased complement activation $\rightarrow$ decreased pain

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<tr>
<td>Navid et al 2014</td>
<td>Single center, Phase 1 trial; 3+3 dose-finding</td>
<td>hu14.18K322A monotherapy</td>
<td>N = 39 pts w/ relapsed/refractory neuroblastoma</td>
</tr>
</tbody>
</table>

MTD: maximum tolerated dose

hu14.18K322A Safety

- Grade 3/4 pain = 68%
- Hypersensitivity = 2.5%
- Capillary leak syndrome = 0%
- Ocular/vision abnormalities = 51%

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<th>Patients</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anghelescu et al 2015</td>
<td>Chart review</td>
<td>Dinutuximab vs hu14.18K322A</td>
<td>Median opioid reqs 2.41 vs 1.57 mg/kg (p=0.019); no difference in anxiolytics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>N = 9 pts on dinutuximab; N = 19 pts on hu14.18K322A</td>
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</table>
131I-MIBG
Relapsed/Refractory Disease

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<tbody>
<tr>
<td>Matthay et al 1998</td>
<td>Single center, Phase 1</td>
<td>131I-MIBG monotherapy</td>
<td>N = 30 pts w/ relapsed neuroblastoma</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>30% partial response, 3% complete response; Median OS 6 mo</td>
</tr>
</tbody>
</table>

- Safety
  - Grade 3/4 thrombocytopenia = 62%
  - Grade 3/4 neutropenia = 46%
Small Molecule Inhibitors

- GD2
- ALK
- NET
- MYCN
- Aurora A Kinase
- Norepinephrine transporter (NET)
- Vanillylmandelic acid (VMA)
- Homovanillic acid (HVA)

References:

NET: Norepinephrine transporter
VMA: Vanillylmandelic acid
HVA: Homovanillic acid
ALK: anaplastic lymphoma kinase
Small Molecule Inhibitors

- ALK mutation most common cause of hereditary neuroblastoma
  - Found in 7-10% sporadic cases
  - Crizotinib = ALK inhibitor; approved 8/2011 for NSCLC

- Increased Aurora A kinase expression correlates w/ inferior outcomes
  - Inhibition may result in MYCN destabilization
  - Alisertib = Aurora A kinase inhibitor; investigational agent

ALK: anaplastic lymphoma kinase
NSCLC: non-small cell lung cancer
## Small Molecule Inhibitor Efficacy

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<tr>
<td>Mosse et al 2013</td>
<td>Multi-center, Phase 1</td>
<td>Crizotinib monotherapy</td>
<td>N = 34 pts w/ relapsed/ refractory neuroblastoma MTD = 280 mg/m²; ORR 29.3% (5.8% complete response, 23.5% stable disease)</td>
</tr>
<tr>
<td>DuBois et al 2016</td>
<td>Multi-center, Phase I</td>
<td>Alisertib + irinotecan + temozolomide</td>
<td>N = 22 pts w/ relapsed/ refractory high-risk neuroblastoma MTD = 60 mg/m²; ORR 31.8% (22.7% complete response, 9.1% partial response); 2yr PFS = 52.4%</td>
</tr>
</tbody>
</table>

MTD: maximum tolerated dose  
ORR: objective response rate  
PFS: progression-free survival
Small Molecule Inhibitor Safety

• Crizotinib
  • Grade 3/4 neutropenia = 12.7%
  • Grade 3/4 transaminitis = 2.5%
  • Visual disturbances = 37%

• Alisertib
  • Any grade thrombocytopenia = 20%
  • Any grade neutropenia = 22%
    • Myeloid growth factor support
  • Any grade diarrhea = 22%
    • Cephalosporin prophylaxis
Case, Revisited

• 6 months after completion of immunotherapy, KE notes a large, palpable mass in her abdomen, concerning for relapse.

• Which of the following treatment modalities exhibited the highest response rates in relapsed/refractory disease?
Self-Assessment #3

- Which of the following treatment modalities exhibited the highest response rates in relapsed/refractory disease?
  
  a. $^{131}$I-MIBG monotherapy
  b. Crizotinib monotherapy
  c. Alisertib combination therapy
  d. hu14.18K322A monotherapy
Pediatric Neuroblastoma: Pharmacotherapy Advances for High-Risk and Relapsed/Refractory Disease

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Dinutuximab Pain Management Algorithm

Morphine infusion

- Patient above pain goal?
  - Yes: Maximize morphine infusion rate
    - Patient above pain goal?
      - Yes: Slow dinutuximab infusion rate
        - Patient above pain goal?
          - Yes: Add adjuncts: gabapentin, dexmedetomidine, lidocaine
    - No: Continue current rate

- No: Continue current rate
  - Patient above pain goal?
    - Yes: Slow dinutuximab infusion rate
      - Patient above pain goal?
        - Yes: Add adjuncts: gabapentin, dexmedetomidine, lidocaine
    - No: Continue current rate
  - No: Continue current rate
    - Patient above pain goal?
      - Yes: Slow dinutuximab infusion rate
        - Patient above pain goal?
          - Yes: Add adjuncts: gabapentin, dexmedetomidine, lidocaine
      - No: Continue current rate

Mayo Clinic Children's Center
Conclusions

• Dinutuximab is standard of care for high-risk neuroblastoma
  • Pain management!

• $^{131}$I-MIBG has been studied in upfront and relapsed/refractory settings
  • Promising response rates, but technical difficulties

• Small molecule inhibitors have been studied in relapsed/refractory setting
  • Alisertib appears to be promising
why do you think this since it was given in combination and to newly diagnosed patients. I would expect the response rate to be higher.
Tumor Biology

NET: Norepinephrine transporter
VMA: Vanillylmandelic acid
HVA: Homovanillic acid
ALK: anaplastic lymphoma kinase

Catecholamines

VMA
HVA

MyCN

Aurora A Kinase